

ARIC Manuscript Proposal #776

PC Reviewed: 03/08/01

Status: A

Priority: 1

SC Reviewed: 03/22/01

Status: A

Priority: 1

1.a. Full Title: Retinal arteriolar diameter and its relation to Incident Hypertension: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Retinal diameter and hypertension

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

This analysis is part of overall objective to investigate the relation of retinal microvascular lesions, graded during the ARIC study Visit 3 and cardiovascular diseases. Specifically, this proposal will be an extension of ARIC #339 (Retinal arteriolar diameter and elevated blood pressure), as we explore the prospective relation of retinal arteriolar diameter to incident hypertension. We estimate that the sample size for this our analysis to be approximately 8,000 persons (persons with gradeable retinal photographs at Visit 3, who participated in the Visit 4 examination).

After approval, the initial analyses and writing will take place between April 2001 and June 2001, final analysis between July 2001 and September 2001, and final writing and submission of manuscript between October 2001 and December 2001.

4. Rationale:

Hypertension is a major treatable risk factor for cardiovascular diseases, affecting up to 50 million adult persons in the United States alone.¹ Large epidemiological studies have shown that even a mild elevation of blood pressure, within the range considered “normal”, may increase risk of coronary heart disease, stroke and cardiovascular mortality.¹

Despite extensive research, much remains to be elucidated regarding the etiology, pathogenesis and natural history of hypertension. Pathologically, hypertension is associated with narrowing of the vascular lumen of the peripheral microcirculation (involving mainly arterioles).² The narrowing in turn may be related to both vasoconstriction and to vascular hypertrophy. Complex mechanisms involving the autonomic nervous system and both circulating and local vasoconstrictor and vasodilator hormones appear to contribute to this narrowing, and possibly to the pathogenesis of hypertension. Furthermore, several traditional (e.g. obesity,^{1,3} low physical activity,⁴ smoking,³ alcohol consumption³) and non-traditional (e.g. plasma fibrinogen⁵, hyperinsulinemia⁶) risk factors for hypertension have been identified, although the relation of these risk factors to the pathophysiology of arteriolar vasoconstriction and hypertension remains unclear.^{2,7,8}

The retinal arteriole offers a unique opportunity to investigate noninvasively the relation of retinal arteriolar caliber to the development of hypertension. The close relation between hypertension and the retinal microvasculature is already well established.⁹ Sustained elevation of blood pressure appears to cause a series of physiological and pathological changes in the retinal microvasculature.¹⁰ One of the earliest signs involves reversible retinal arteriolar vasoconstriction. With continued elevation of blood pressure, the arteriolar narrowing possibly becomes permanent, as arteriosclerosis and other processes sets in. Severe retinal microvascular damage occurs with subsequent ischemia and breakdown of the blood-retinal barrier, resulting in retinal hemorrhage and micro-infarctions (soft exudates). The presence of retinal microvascular damage appears to be a marker for target organ damage elsewhere in the body.⁹ It is not clear, however, if retinal arteriolar narrowing predicts future increases in blood pressure and clinically defined and overt hypertension.

In the ARIC study, retinal microvascular characteristics were graded from retinal photographs taken at Visit 3. In addition, arteriolar calibers were quantified based on a standardized computer-assisted measurement of individual retinal arterioles and venules. We have previously shown that retinal arteriolar diameter is a sensitive marker of current blood pressure levels, and also of past blood pressure levels, independent of current blood pressure, suggesting that retinal arteriolar caliber reflects persistent damage from long term elevated blood pressure.¹¹

In this present analysis, we will evaluate whether retinal arteriolar caliber predicts future blood pressure levels and incident hypertension. This information would provide further insights into the relation of arteriolar caliber to the risk of hypertension.

5. Main Hypothesis/Study Questions:

- (1) After controlling for age, sex, race, field center, mean arterial blood pressure levels at Visits 1 to 3, other hypertension risk factors (e.g. education, BMI, waist / hip ratio, smoking, alcohol consumption, physical activity), smaller retinal arteriolar diameter at Visit 3 is associated with incident hypertension (from Visit 3 to 4)
- (2) After controlling for similar factors in (1), smaller retinal arteriolar diameter at Visit 3 is associated with greater increase in systolic, diastolic and mean arterial blood pressure (from Visit 3 to 4)

6. Data (variables, time window, source, inclusions/exclusions):

- (1) Retinal variables: Retinal arteriolar diameter, quantified as branch retinal arteriole-to-venular ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent. Focal retinal microvascular changes include arteriovenous nicking, focal arteriolar narrowing, any retinopathy, retinal hemorrhage and type of hemorrhage (flame-shaped and blot hemorrhage), microaneurysm, soft exudates and hard exudates.
- (2) Demographic variables: age at visit 3, sex, race, field center
- (3) Hypertension / Blood pressure indicators: Hypertension status, mean arterial BP, systolic and diastolic BP, hypertensive medications, at Visits 1-4.
- (4) Other hypertension / CVD risk factors: Education, BMI, waist / hip ratio, physical activity score, diabetes status, fasting glucose levels, serum lipids (total, HDL and LDL cholesterol, TG, lp(a), apo A1 and B), hemostatic function indicators (von Willebrand factor, factor VIIIc, fibrinogen), WBC, cigarette smoking indicators (ever/never, current/former/never, pack-years), alcohol indicators, diabetic medications, (variables from ARIC Visits 1-4, except for lp(a), apo A1 and B, von Willebrand factor, factor VIIIc, and cigarette pack-years, available from ARIC visit 1 only)

(5) Exclusion criteria: From participants at ARIC Visit 3, exclude persons who did not participate in the second exam, whose race is neither black nor white, if missing data on BP, and hypertension status, at Visits 1 to 4. Also exclude persons with no retinal photographs or upgradeable photographs and those with retinal venous or artery occlusions.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes No

b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? Yes No

(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? Yes No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? Yes No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://bios.unc.edu/units/csc/ARIC/stdy/studymem.html> Yes No

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